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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,160	05/01/2001	Hiroyuki Mizuguchi	081356-0163	2644

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/02/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/845,160	Applicant(s) MIZUGUCHI ET AL.	
	Examiner Ulrike Winkler, Ph.D.	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Drawings

The drawings have been approved by the Draftsperson's.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-6, 9, 11-14 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Dmitriev et al. (Journal of Virology, 1998).

The instant invention is drawn to a product and a method of making the product. The product is an adenovirus fiber mutant ~~and~~ whereby a unique restriction site is inserted into the gene sequence coding for the fiber HI loop allowing for the insertion of foreign peptides into the loop region. The peptides that are inserted into the loop region will convey tropism for vascular endothelial cells of a tumor (claims 3, 4, 11, 12). The foreign peptide contains the tripeptide RGD (claims 5, 6, 13, 14).

Dmitriev et al. disclose a method of producing a recombinant adenovirus that will have altered tropism by inserting a unique restriction site (EcoRV) into the fiber HI knob of the adenovirus. The reference discloses incorporating the tripeptide RGD into the peptide of the HI loop of the recombinant adenovirus (see material and methods). The sequence encoding the

tripeptide is inserted into the fiber sequence using the unique restriction site that was engineered into the virus. The ability of the virus to infect cells that do not posses the coxsackievirus and adenovirus receptor (CAR) was tested. The recombinant viruses were able infect human umbilical vein endothelial cells and human embryonal rhabdomyosarcoma cells. Experiments showed that in this model Ad-RGD fiber was able to direct levels of transgene expression 2-3 orders of magnitude higher than those mediated by control virion containing unmodified fibers. These results strongly suggest that recombinant Ad vectors containing fibers with genetically incorporated RGD peptides may be ~~of~~ utilized in the context of cancer gene therapy approaches based on *in vivo* gene delivery. Over- expression of several types of integrins in tumor vasculature suggests that derivatives of Ad-RGD expressing therapeutic genes may be utilized for eradication of tumors via abrogation of their blood supply (see page 9712, 2nd column, lines 3-18). Therefore, the instant invention is anticipated by Dmitriev et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dmitriev et al. (Journal of Virology, 1998) in view of Arap et al. (Science, 1998).

The instant invention is drawn to a product and a method of making the product. The product is an adenovirus fiber mutant ~~and~~ whereby a unique restriction site is inserted into the gene sequence coding for the fiber HI loop allowing for the insertion of foreign peptides into the loop region. The unique restriction sites are Csp45I and/or ClaI (claims 2, 10, 18). The peptides that are inserted into the loop region will convey tropism for vascular endothelial cells of a tumor (claims 3, 4, 11, 12). The foreign peptide will contain the tripeptide RGD (claims 5, 6, 13, 14) or the foreign peptide will contain the tripeptide NGR (claims 7, 8).

Dmitriev et al. teach a method of producing a recombinant adenovirus that will have altered tropism by inserting a unique restriction site (EcoRV) into the fiber HI knob of the adenovirus. The reference discloses incorporating the tripeptide RGD into the peptide of the HI loop of the recombinant adenovirus (see material and methods). The sequence encoding the tripeptide is inserted into the fiber sequence using the unique restriction site that was engineered into the virus. The ability of the virus to infect cells that do not posses the coxsackievirus and adenovirus receptor (CAR) was tested. The recombinant viruses were able infect human umbilical vein endothelial cells and human embryonal rhabdomyosarcoma cells. Experiments showed that in this model Ad-RGD fiber was able to direct levels of transgene expression 2-3

orders of magnitude higher than those mediated by control virion containing unmodified fibers. These results strongly suggest that recombinant Ad vectors containing fibers with genetically incorporated RGD peptides may be utlized in the context of cancer gene therapy approaches based on *in vivo* gene delivery. Over- expression of several types of integrins in tumor vasculature suggests that derivatives of Ad-RGD expressing therapeutic genes may be utilized for eradication of tumors via abrogation of their blood supply (see page 9712, 2nd column, lines 3-18). The reference does not teach utilizing the Csp45I and/or ClaI restriction sites of the tripeptide NGR.

Arap et al. teach a phage a display library to screen peptides that home to tumors. Endothelial cells in the angiogenic vessels within solid tumors express several proteins that are absent or barely detectable in established blood vessels, including alpha integrins and receptors for certain angiogenic growth factors (see intro). To determine whether *in vivo* selection could be used to target tumor blood vessels, we injected phage peptide libraries into the circulation of nude mice bearing human carcinoma xenografts. Recovery of phage from the tumors led the identification of peptide motifs that targeted the phage into the tumors. One motif contained the sequence RGD sequence and another motif contained NGR. Two other sequences containing the NGR were also tested. Tumor homing for all three peptides was independent of the tumor type and species (page 377, 3rd column, 1st paragraph). The homing ratio of the phage displaying the NGR motif was three times that of the RGD-4C phage (page 378, 1st column, 1st paragraph). It is expected that the NGR and RGD-4C motif target human vasculature as well, because the NGR phage binds to blood vessels of human tumors and less so than to vessels in normal tissue (page 380, 1st column, 2nd paragraph). The reference teaches phage display (phage are viruses that

effect bacteria) of tripeptides that are targeted to tumor endothelial cells, the reference teaches the tripeptide RGD and NGR. The reference also teaches that tumor homing is more efficient with the NGR tripeptide. The reference does not teach inserting the tripeptides into an adenoviral vector.

It would have been obvious to one of ordinary skill in the at the time the invention was made to utilize a unique restriction site in an adenoviral vector in order to insert a foreign peptides into the HI fiber loop in order to alter the viruses tropism, ie. the ability to infect cells that are not within its natural range as taught Dmitriev et al. One having ordinary skill in the art would have been motivated to do this in view of the teachings of Arap et al. which show the tripeptide homing in a bacterial viral system which teaches that the NGD tripeptide is more efficient at tumor homing. Furthermore, it is well known in the art to utilize unique restriction sites that may be cloned into a vector for the ease of inserting gene sequences into the site. The key element is choosing a unique site as taught by Dmitriev et al., here the choice is based inserting a restriction site that is not present in the virus or peptide sequence. A scan of two adenoviral genomes indicted that there are several restriction sites that are not present in the adenovirus. These not only include Csp45I, Cla1 but also include VspI, Swa1, SmiI, PacI, BspDI, CpoI, Ban III, SrfI to name a few. Therefore, the specific choice of a unique restriction enzyme sequences such as Csp45I and/or ClaI would fall within the skills of an ordinary artisan because the choice is based on the sites that are not present in a particular viral sequence. If the choice of restriction enzyme produces an unexpected result, applicant needs to point out what the unexpected results are. Therefore, the instant invention is obvious over Dmitriev et al. in view of Arap et al.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

U.S. Pat. No. 6,210,946 B1.

Krasnykh et al. Characterization of an adenoviral vector containing a heterologous peptide epitope in the HI loop of the fiber knob. Journal of Virology (1998), Vol. 72, No. 3, pp. 1844-1852.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D. 9/26/10